January 31, 2002

Edwin L. Mongan III
E.I. du Pont de Nemours & Co., Inc.
1007 Market Street
Wilmington, DE 19898

Dear Mr. Mongan:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Dinitriles category, posted on the ChemRTK Web Site on September 13, 2001. I commend DuPont for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

In addition to the attached comments, EPA would like to note that the conduct of dermal and eye irritation studies are not a part of the HPV Challenge Program. However, we would like to emphasize that sponsors should use all existing data to support their proposed categories. In addition, we request that sponsors defer any proposed testing until after public comments have been received.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that DuPont advise the Agency, within 90 days of the posting on the Chemical RTK website, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Dinitrile Category

SUMMARY OF EPA COMMENTS

The sponsor, E.I. du Pont de Nemours & Co., Inc., submitted a test plan and robust summaries to EPA for the dinitriles category dated July 11, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 13, 2001. Dinitriles included in this group are adiponitrile (ADN) (CAS No. 111-69-3), 2-methylglutaronitrile (2-MGN) (CAS No. 4553-62-2), and ethylsuccinonitrile (ESN) (CAS No. 17611-82-4).

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical and Environmental Fate Data. Because the branched members of the category may be more resistant to biodgradation, EPA suggests that a biodegradation test be conducted on ESN rather than extrapolating from ADN. The Submitter should make sure that its reported Partition Coefficient for ESN (0.28) is reasonably accurate or provide measured data.

2. Health Effects Endpoints. The overall data provided to support a category approach for health endpoints is weak. However, the structural similarities of the chemicals would suggest a similar hazard profile. Genotoxicity was the only health effects endpoint adequately addressed for all category members. The ongoing repeated-dose toxicity study on 2-MGN should lend additional support to the category approach.

3. Ecological Effects. Ecological effects data and SAR estimations for all three endpoints as a category approach are adequate for these chemicals. The submitter needs to provide missing data elements in a number of robust summaries.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON DINITRILES CATEGORY CHALLENGE SUBMISSION

Category Definition

The dinitrile category is composed of three hexanedinitrile isomers. Each isomer differs in the position of one of the nitrile groups on a straight carbon chain. The Submitter lists the members of this group as adiponitrile, 2-methylglutaronitrile, and ethylsuccinonitrile.

Category Justification

The submitter supports grouping these dinitriles based on their similar structural and physico-chemical properties, environmental fate characteristics, and health and environmental effects.

The measured and estimated physical property values provided for the three dinitriles adequately support the grouping of these compounds with the exception of melting point. The differences in melting point are likely associated with molecular symmetry and are not anticipated to affect environmental behavior.

The submitter states that the dinitriles in this category are expected to exhibit similar environmental behavior. This expectation is supported by the estimated bioaccumulation and fugacity values provided by the submitter. The submitter also anticipates that biodegradation will be similar for all category members and provides data for ADN. Although the structural similarities between these compounds

suggest that the nitrile moieties will have similar biodegradation pathways, the presence of alkyl branches in 2-MGN and ESN may affect their biodegradation rates and, by extension, their persistence in the environment. Therefore, support for grouping these chemicals on the basis of environmental behavior in the absence of additional biodegradation information is weak.

The available health effects data provide weak support for a category approach. The test plan suggests that reported acute toxicity information supports the category approach. While the oral acute toxicity studies reported similar ranges of lethality, no data were provided for target organs or non-lethal endpoints. When completed, data from the ongoing repeated-dose study for 2-MGN will allow a more complete comparison to existing data for ADN. Given the similar molecular structures, marked differences in toxicity are not expected.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The Partition Coefficient value for ESN (0.28) differs significantly from the Partition Coefficients for ADN (-0.32) and 2-MGN (-0.644). The submitter needs to reconcile this difference or provide measured Partition Coefficient data for ESN.

Environmental Fate (Photodegradation, Stability in Water, Biodegradation, Fugacity)

EPA agrees with the submitter's test plan for these endpoints except for biodegradation. It is likely that the alkyl branches of 2-MGN and ESN may affect their biodegradation rates; therefore, EPA suggests that one of the branched members be tested, preferably ESN.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

The submitter is currently conducting a 4-week inhalation study of 2-MGN, and has proposed dermal and eye irritation studies of ESN. Dermal and eye irritation studies are not endpoints of the HPV Challenge Program.

Acute and Repeat Dose Toxicity. For ADN, adequate health effects summaries were provided for all HPV Challenge endpoints. For the other two category members, sufficient information is not available to allow either an evaluation of their toxicities or a reliable comparison with ADN. For ESN and 2-MGN, robust summaries were provided only for gene mutations and acute toxicity studies. The repeated-dose testing of 2-MGN (ongoing) is appropriate and may be sufficient to address this endpoint, if the results are comparable to those of ADN.

Genetic Toxicity Data. EPA agrees that this endpoint has been adequately addressed.

Reproductive and Developmental Toxicity. Adequate developmental and reproductive toxicity information is available for ADN. If the ongoing study on 2-MGN indicates dissimilar toxicities, the submitter needs to consider testing either 2-MGN or ESN for these endpoints.

Ecological Effects (Fish, daphnid and algal toxicity)

Fish. The submitter provided one fish LC50 study for ADN and SAR predicted values using ECOSAR for

all category members. Gathered in-house data reported a chemical purity of 99 percent for ADN, and a confidence limit of 95 percent for the acute toxicity value for fish. No additional testing for this endpoint is proposed in the test plan. Per HPV Challenge guidance this approach, in this case, is acceptable.

Aquatic Invertebrates. Athough the 24-hour daphnia test submitted for 2-MGN is invalid due to the exposure duration (24-hour versus the standard 48-hour duration), the remaining two daphnia tests for ADN, ESN and supporting SAR data satisfy the category approach.

Algae. The submitter provided one summary of a toxicity study for ADN in algae and SAR predicted values using ECOSAR for all category members. No additional algal toxicity testing is proposed. Per HPV Challenge guidance this approach, in this case, is acceptable.

Specific Comments on the Robust Summaries

Health Effects

Acute toxicity

For the robust summaries of acute oral toxicity studies for 2-MGN and ESN, the sponsor needs to provide additional information, including the number and gender of animals tested, the use of controls, the length of the post-observation period, and/or endpoints tested. Based on the information provided, the study design for ESN was inadequate because too few animals were used.

Genetic toxicity

For the robust summary of the bacterial reverse mutation assay for 2-MGN, the sponsor needs to provide additional information, including potential contaminants in the test substance (purity 85%) and the number of replicates tested.

For the robust summary of a mouse micronucleus test for 2-MGN, the sponsor needs to provide additional information, including the use of negative controls and method details.

Repeated dose toxicity

For the robust summary of the repeated-dose oral toxicity study for ADN, the submitter needs to provide additional information, including clinical signs, clinical chemistry, and necropsy.

Ecotoxicity Studies

All SAR robust summaries failed to provide the octanol/water partition coefficient information by source and the value entered into the ECOSAR program.

Aquatic Invertebrates. Missing data elements needed for the ADN study are chemical purity, hardness, and pH and for the ESN study hardness and dissolved oxygen.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.